REMARKS

Claims 1-14, 17-23 and 25-31 were pending in the instant application. By this Amendment, Applicants have canceled claims 10 and 30-31 without prejudice to future presentation. Applicants have amended claims 1, 3, and 25 and have added new claims 32 and 33. Support for the amendments and new claims can be found in the specification and claims as originally filed. Specifically, support for the amendment to claim 1 can be found, *inter alia*, at page 6, line 32 to page 7, line 1, and at page 10, lines 25-30 in the specification. Support for the amendment to claim 3 can be found, *inter alia*, at page 6, line 32 to page 7, line 1 and page 10, lines 25-30 and at page 9, line 23. Claim 25 has been amended merely for clarity. Support for new claims 32-33 can be found, *inter alia*, at page 10, line 38 to page 11, line 10, and at page 13, lines 27-29. The present Amendment does not introduce any new matter, and thus, its entry is requested. Upon entry of the present Amendment, claims 1-9, 11-14, 17-23, 25-29, and 32-33 will be pending and under examination.

Request for Examiner's consideration of previously submitted references

Applicants seek confirmation from the Examiner that the references submitted in the Information Disclosure Statement filed October 7, 2003 have been made of record and considered by the Examiner in connection with this application.

Examiner's Rejection under 35 U.S.C. 112, second paragraph

Claims 1-23 and 25-26 were rejected as indefinite for reciting "in vitro biological activity." Specifically, the Examiner was of the opinion that the phrase is indefinite because it is unclear which of the biological activities recited in the specification (*in vitro* antiviral, antiproliferative, and immunomodulatory activities) are being retained in the claimed formulation. The Examiner further noted that the specification sets forth inhibition of the cytopathic effect of a virus as the method chosen to determine the biological activity. The Examiner had indicated that the rejection can be

overcome "by reciting the biological activity for which there is support in the instant specification." Claims 1 and 3 have been amended to recite liquid formulations having stability of biological activity or methods of stabilizing the biological activity of said formulations, wherein the biological activity is inhibition of viral cytopathic effects. In the Advisory Action, the Examiner indicated that these claim amendments, which were previously submitted but not entered, would be sufficient to overcome the rejection under 35 U.S.C. §112, second paragraph. Accordingly, Applicants respectfully request that the amendments now be entered and that the Examiner reconsider and withdraw the rejection.

Examiner's Rejection under 35 U.S.C. 102(b)

The Examiner has maintained the rejection of claims 1, 2, 4-8, 13-14, and 21-23 under 35 U.S.C. §102(b) as being anticipated by EP 0529 300 B1. The position taken by the Examiner in the Office Action was that the phrase in claim 1-- "optionally, at least one physiologically acceptable preservative"--encompasses human serum albumin, and thus, the claim was anticipated by the disclosure of formulations that include human serum albumin. In the Advisory Action, the Examiner indicated that deleting the above phrase would not be sufficient to overcome the anticipation rejection because the claim would still fail to recite the exclusion of human serum albumin from the formulations.

In response, without conceding the correctness of the Examiner's position, but to expedite allowance of the subject application, Applicants have removed the phrase noted above from claim 1, and additionally amended the claim to specifically recite that the claimed formulations do not contain human serum albumin. Accordingly, the rejection under 35 U.S.C. §102(b) now has been obviated as EP 0529 300 B1 does not refer to a liquid pharmaceutical formulation as recited in the claims. Applicants, therefore, respectfully request that the Examiner reconsider and withdraw this rejection.

Examiner's Rejection under 35 U.S.C. 103(a)

The Examiner has maintained the rejection of claims 1-14, 17-23 and 25-31 under 35 U.S.C. §103, as being obvious over the EP 0529300 reference and the Patel patent of record (U.S. Patent No. 5,358,708). The Examiner has taken the position, as above, that recitation of the phrase "and, optionally, at least one physiologically acceptable preservative" encompasses the addition of stabilizers, including human serum albumin and methionine. The Examiner has also indicated that Patel's use of methionine to stabilize interferon-α formulations would have motivated one of skill in the art to use such a stabilizer to stabilize interferon-β formulations, such as those claimed by Applicants.

In response, without conceding the correctness of the Examiner's position, but to expedite allowance of the instant application, Applicants have amended claim 1 to recite formulations that consist essentially of human interferon-β and a buffer, wherein the concentration of the interferon-β is less than 12 $x10^6$ units/ml. In addition, Applicants have removed the phrase noted above from both claims 1 and 3, and have amended these claims to specifically recite that the claimed formulations do not contain human serum albumin. Claim 1, as amended, and those which depend therefrom, therefore excludes formulations which contain HSA or other stabilizers. EP 0529 300 B1 does not teach or suggest human serum albumin-free, stabilizer-free formulations that contain β interferon at concentrations less than 12 $x10^6$ units/ml. Therefore, even if one were to combine the EP reference with Patel, as the Examiner has done, one would not arrive at Applicants' claim 1, because as Patel's supposed relevance is in its suggestion to use methionine to stabilize interferon formulations, a combination of these references would result in a formulation containing such stabilizers. As stated, Applicants' claim 1 excludes such formulations by using "consisting essentially of" terminology.

Moreover, Applicants respectfully point out that Patel does not teach or suggest interferon-β at all, but rather formulations containing interferon-α and stabilizers, such as methionine, which are described as appropriate for that particular interferon form. The Examiner essentially takes the position that these two different interferon forms are sufficiently similar to lead one of ordinary skill

in the art to reasonably conclude that stabilizers appropriate for formulations containing the α form would also be appropriate for formulations containing the β form. Applicants assert that, to the contrary, it is not obvious to the skilled person that the methionine stabilization of interferon-α (IFN-α) can be applied to interferon-β (IFN-β).

Patel discloses liquid interferon-α-2b formulations from *E. coli* in a citrate/phosphate buffer with a pH of 6.9 and 2 mg/ml methionine (see column 4, Example 1). The shelf life was tested at 40°C over a period of 2 weeks. At the end of this period, the activity measured just over 80% of the starting activity, while the control sample, without methionine, measured just over 70% (Figure 1). However, one of ordinary skill in the art would not have reasonably expected that methionine could be successfully used to stabilize IFN-β formulations, based simply on methionine's activity with respect to IFN-α. This is so, particularly because there are a number of fundamental physical and chemical differences between interferon-α and -β, which are crucial for each one's stability and chemical integrity. In fact, Patel itself recognizes this. As pointed out previously, Patel states at column 2, lines 52-57, that the three major human interferons that have been identified, namely interferon-α, interferon-β, and interferon-γ, each possess different antigenic and physicochemical properties and are derived from different cellular sources, in response to different inducers. The following publications, copies of which are attached to this Amendment, further support this:

- Sehgal and Sagar, "Comparative Analysis of Interferon Structural Genes" in *Interferons and Their Applications* (Ed. Came and Carter), Springer 1984, pages 65-77;

- Zoon and Wetzel, "Comparative Structures of Mammalian Interferons" in *Interferons and Their Applications* (Ed. Came and Carter), Springer 1984, pages 79-100;

- Powell, "A Compendium and Hydropathy/Flexibility Analysis of Common

Reactive Sites in Proteins: Reactivity at Asn, Asp, Gin and Met Motifs in Neutral pH Solution" in *Formulation, Characterization, and Stability of Protein Drugs* (Ed. Pearlman and Wang), Plenum Press 1996, pages 1-139; and

- Lin et al., "Interferon-β-1b (Betaseron®): A Model for Hydrophobic Therapeutic Proteins" in: *Formulation, Characterization, and Stability of Protein Drugs* (Ed. Pearlman and Wang), Plenum Press 1996, pages 275-301.

These documents reveal, among other things, that the amino acid sequences of IFN-α_2 and IFN-β have a homology of only 35% (57 out of 166 amino acids matching, see Figure 1 of Sehgal and Sagar). The homology between IFN-α_1 and IFN-β is 32% (Sehgal and Sagar, Figure 1). This low sequence identity further supports Applicants' contention that one of skill could not have reasonably concluded that the same stabilizers would be effective for different interferon forms. More specifically, Patel's disclosure of any particular stabilizers effective in extending storage life of IFN-α-2b formulations simply does not result in an expectation that the same effectiveness would occur in IFN-β formulations. These facts alone should be sufficient to overcome the Examiner's obviousness rejection.

Nevertheless, Applicants point out further reasons why the Examiner's rejection is improper. Applicants note that claim 3, as amended, recites a formulation in which the IFN-β is glycosylated. This glycosylation is a further fundamental difference between IFN-α and IFN-β. Natural IFN-α is made up of various sub-types which are, almost without exception, non-glycosylated proteins. However, only one sub-type is known for native IFN-β, and it is glycosylated (Sehgal and Sagar, page 67, last paragraph; Zoon and Wetzel, page 93). The stability tests in Patel are based on recombinant IFN-α-2b from *E.coli* (column 3, top), which is not glycosylated. Non-glycosylated IFN-β from *E.coli* is known from the prior art (Powell, pages 80, et seq.) and its biological activity differs only slightly from the glycosylated form. The glycosylated form can be obtained from CHO cells. There are, however, significant differences in solubility between glycosylated interferon-α and

non-glycosylated and glycosylated interferon-β, as the following summary table shows:

Table: solubility of interferon-α and interferon-β

	Glycosylation	Soluble at neutral pH
IFN-α	no	yes
IFN-β	no	no
IFN-β	yes	yes

For example, the non-glycosylated form of IFN-β is not soluble under the same conditions as interferon-α because the former has a strong hydrophobic character (Lin et al., page 290, section 7.1.1). The documents cited above were available when the present application was filed, so the solubility properties of recombinant IFN-β as revealed in these references would have been known to the skilled artisan at that time. The skilled person would therefore have had significant doubts from the outset regarding the applicability of the teaching of Patel to glycosylated interferon-β. In particular, he would have had no reason to predict that methionine would have any stabilizing effect on glycosylated interferon-β based on a teaching of its use in a formulation containing non-glycosylated interferon-α. The effect of methionine could not have been accurately predicted because the non-glycosylated form of interferon-β, which is structurally more closely related to interferon-α than the glycosylated form of interferon-β, is not soluble under a physiological pH as required in the formulations of the present invention. Because methionine's effect on non-glycosylated IFN-β is impossible to predict, methionine's effect on glycosylated IFN-β is also impossible to predict. The skilled artisan therefore would have been instead motivated to refer to other known methods for obtaining liquid interferon-β formulations, not teachings such as Patel, which refer only to the α form. (Such alternate methods would have included keeping non-glycosylated IFN-β at a neutral pH in solution by means of detergents (e.g. 0.1% SDS) or chaotropic salts (e.g. 4 M guanidinium-HCl), applying an acidic or strongly alkaline pH, (Lin et al., page 290),

or adding human serum albumin at a neutral pH to achieve a solution (Lin et al., page 293, last paragraph)).

Patel offers still further evidence that its teachings would not be applicable here. For example, in column 4, line 8-9 of Patel, it is stated:

> "It should be apparent that different proteins will become inactivated during storage at different rates and under different conditions, due to chemical differences between the proteins."

In column 4, line 14 it is further stated:

> "Also, the storage-prolonging effects of methionine and histidine are not equivalent with the different proteins and, of course, mixtures of the amino acids will exhibit different effects as the ratio is varied, the identity of the protein is changed and/or the concentrations are altered."

These assertions are confirmed by the experimental data from IFN, GM-CSF and IL-4, which show degradation to greatly varying degrees within 2 weeks. This clearly adds support to Applicants' contentions that the teachings of Patel are not applicable to proteins other than those taught therein. Accordingly, one familiar with the art would have had no motivation to select and combine the references as the Examiner has done. Applicants therefore assert that Applicants' claims are not rendered obvious by the cited art and respectfully request that the Examiner reconsider and withdraw the rejections under 35 U.S.C. §103.

In view of the above remarks and amendments, Applicants believe that the Examiner's rejections set forth in the June 26, 2003 Office Action have been fully overcome and that the present application is in condition for allowance. The Examiner is invited to telephone the undersigned if

it is deemed to expedite allowance of the application.

Respectfully submitted,

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Attachments
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